AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0002] with the following amended paragraph:

[0002] The present invention generally relates to methods for aiding in the diagnosis of dysautonomic disorders and dysautonomic conditions and methods for treating individuals diagnosed as having a dysautonomic disorder or a dysautonomic condition. More particularly, the invention relates to a diagnosis method comprising analyzing a stool sample of an individual for the presence of a biological marker (or marker compound) that provides an indication of whether the ~~invidual~~ individual has, or can develop, a ~~dysuatonic~~ dysautonomic disorder or dysautonomic condition, as well as a ~~therapuetic~~ therapeutic method for treating a dysautonomic disorder or dysautonomic condition by administration of, e.g., secretin, neuropeptides, peptides and/or digestive enzymes.

Please replace paragraph [0003] with the following amended paragraph:

[0003] Familial Dysautonomia (FD), which is also known as Riley-~~day~~ Day syndrome, is an autosomal recessive sensory neuropathy that affects approximately 1 in 4,000 individuals of Ashkenazi Jewish descent. This disorder is marked by a reduction of unmyelinated and small myelinated fibers as well as a reduction of dopamine-beta-~~hyrozylase~~ hydroxylase in the ~~bood~~ blood. FD decreases both the sympathetic neurons and the peripheral small fibers that modulate temperature regulation. It is thought to arise from both the failure of intrauterine development of neurons and their postnatal development. ~~Symaptomotology~~ Symptomology of FD includes, ~~e.g.,~~ renal disease, corneal ulcerations, mental retardation, loss of pain and vibratory senses, ~~in coordination~~ incoordination of movements, diarrhea, esophageal reflux, secretory diarrhea, gastrointestinal paresis, hypotension, facial abnormalities, altered dentition, increased salivary secretion, abnormalities of the sweat glands, bowel distension, fecal impaction, prolonged QT intervals (>440), risk of sudden death, and orthostatic syncope. Further features include decreased pain sensation, decreased temperature regulation, difficulty feeding, lack of overflow tears while crying, recurrent pneumonias, scoliosis or ~~hyperkyhsis~~ hyperkinesis, increased

sweating and skin blotching, decreased stature, as well as other conditions associated with autonomic dysfunction.

Please replace paragraph [0004] with the following amended paragraph:

[0004] Currently the underlying biochemical and genetic defects which cause the FD disorder are unknown. The gene which causes this disorder has been mapped to chromosome 9, in the q31-33 region. Presently, there is no prenatal screening test for this condition, and there is no early detection of the condition other than the presence of ~~symptomotology~~ symptomology.

Please replace paragraph [0005] with the following amended paragraph:

[0005] There are a plethora of ~~dysautonmic~~ dysautonomic disorders and/or disorders in which symptomologies of autonomic dysfunction are manifest. For instance, Parkinson's disease is marked by mild to severe autonomic dysfunction, including changes in gait, tremor, discoordination, increased salivary flow, and overall loss of autonomic function. Additionall, changes in executive function are typically noted in a Parkinson's patient, often times allowing the patient to appear as having Alzheimer's ~~disearse~~ disease and resulting in misdiagnosis. Executive function disorders are also found in autistic children.

Please replace paragraph [0006] with the following amended paragraph:

[0006] It is known that Parkinson's disease is caused by a deficient state of levo-dopamine in the brain. More specifically, levo-dopa induced dyskinesis in Parkinson's patients is thought to be a result of denervation of the substantia nigra. To this date, medical science has not found a substrate that would allow an injectable form of ~~l-dopa~~ L-dopa to reach the brain and successfully cross the blood brain barrier. The current dopamine replacement therapy is aimed at either direct replacement or mimicking the action at the dopamine receptor sites in the brain. Sinemet~~TM~~ ™ and Sinemet CR ~~TM~~ ™ are the two major drugs suited to that end. While the

levodopa-therapy can create some ~~benficial changs~~ beneficial changes initially, those changes generally wane over time, and produce other problems such as severe sleep disturbance, dyskinesias, and constant nausea. Medical approaches to Parkinson's disease include surgical destruction of the tissue of the brain and the insertion of microelectrodes (deep brain electrical stimulation) to effected portions of the brain. The insertion of electrodes has the advantage of being reversible. These interventions, however, are generally transient and neither produce a permanent change in the ~~Parkinsonsian~~ Parkinsonian state nor reverse the effects of the disease.

Please replace paragraph [0007] with the following amended paragraph:

[0007] Parkinson's disease is widespread throughout the Western hemisphere and was first reported by physician James Parkinson in 1817. ~~Parkison's~~ Parkinson's disease is first detected as a tremor in a limb, and ultimately progresses to include 3 ~~manifestatons~~ manifestations: (i) rigidity, which is characterized by "cog-wheel" like movement and "lead-pipe" rigidity; (ii) bradykinesia or slowness in movement, and (iii) postural instability associated with a stooped stance and an impaired gait. These altered movements are features of the motor dysfunction, but in addition there can ~~also~~ be a mental impairment in as many as 40% of all Parkinson's patients.

Please replace paragraph [0008] with the following amended paragraph:

[0008] Some authors suggest that Parkinson's disease is a multifactor neurodegenerative disorder, which evolves due to ~~excesive~~ excessive oxidation. The substantia nigra is susceptible to oxidative damage, which supports this theory of the formation of Parkinson's disease. Abnormalities of the oxidative ~~phospherlation~~ phosphorylation impair the mitochondria of the substantia nigra, and intensify free radical generation.

Please replace paragraph [0010] with the following amended paragraph:

[0010] Guillaine-Barre Syndrome (GBS) is characterized as an acute autoimmune polyradiculopathy. It generally manifests as a flaccid paresis coupled with areflexia, sensory loss and disturbance, as well as an elevated ~~cerebrospnal~~ cerebrospinal fluid protein level. There are multiple variations of GBS, each of which displays a specific subgrouping of symptoms, including those of the ~~Miler~~ Miller Fisher Syndrome group. GBS seen primarily in the United States constitutes a subtype best characterized as a demyelinating type. In the past, GBS was thought to be caused by numerous factors such as the presence of an antecedent viral infection. The most recent hypothesis points to the presence of an antecedent infection of Campylobacter jejuni gastroenteritis. It is further postulated that the presence of this infection produces inflammation of the brain and nervous system and gastrointestinal tract.

Please replace paragraph [0012] with the following amended paragraph:

[0012] Furthermore, tumors of differing types can also produce dysautonomic ~~symptomotology~~ symptomology. For example, pheochromocytoma is a well-encapsulated, lobular, vascular tumor, which can occur anywhere in the body. It is made up of chromaffin tissue of the adrenal medulla, or sympathetic paraganglia. Hypertension is the most apparent symptom, reflecting the increased secretion of epinephrine and norepinephrine, and may be either persistent or intermittent. Attacks may occur anywhere from every few months to several times daily, and typically last less than five minutes. Physical and emotional stresses can initiate an attack. During severe attacks, patients may experience headache, sweating, apprehension, palpation, tremor, pallor or flushing of the face, nausea and vomiting, pain in the chest and abdomen, and paresthesias of the extremities, weight loss, and orthostatic hypotension. Inflammation is a hallmark of this condition. Interestingly, these symptoms are common to many other dysautonomic conditions. Chemodectoma is another type of tumor, characterized as any benign, chromaffin-negative tumor of the chemoreceptor system. The most common types of chemodectoma are the carotid (the principal artery in the neck) body tumor and the glomus jugulare tumor, and it is also known as nonchromaffin paraganglioma.

Please replace paragraph [0016] with the following amended paragraph:

[0016] Aromatic L-Amino Acid Decarboxylase Deficiency is a disorder ~~cuased~~ caused by a deficiency of an enzyme of the lyase class that catalyzes the decarboxylation of aromatic amino acids, notably converting dopa to dopamine, tryptophan to triptamine, and hydroxytryptophan to serotonin. The enzyme is then bound to a pyridoxal phosphate cofactor and occurs particularly in the liver, kidney, brain and vas deferens. Symptoms of the disease may include temperature instability, ptosis of the eyelids, hypersalivation, distal chorea, swallowing difficulties, drowsiness, irritability, truncal hypotonia, oculogyric crises, and pinpoint pupils.

Please replace paragraph [0018] with the following amended paragraph:

[0018] Familial Paraganglioma Syndrome is another tumor related disease. Due to the chemoreceptor function of the carotid body ~~these~~, these tumors were first called chemodectomas or carotid body tumors, though ~~carotidy~~ carotid body ~~paragnanglioma~~ paraganglioma is the most accurate terminology for these lesions. ~~Paragnaglioma~~ Paraganglioma tumors that develop from the paraganglia adjacent to the vagus nerve and the jugular bulb are usually described as glomus vagale and glomus jugulare. Paraganglioma tumors are quite rare and account for less than 1000 ~~reports~~ reported cases since 1980.

Please replace paragraph [0028] with the following amended paragraph:

[0028] One theory for the cause of SIDS points again to the role of reflux. Once thought to be a normal postmortem finding, the evidence of gastro-~~espohageal~~ esophageal reflux postmortem indicates this as a possible contributory factor. Other theories point to the role of nerve damage or nerve malfunction as playing a contributory role in the formation of SIDS. One study demonstrates a marked prolonged QT interval in those who are at risk for SIDS. Researchers have documented that a child having a SIDS "attack" who was brought to the hospital was

suffering from a prolonged QT interval. Even though the child survived the episode, it revealed an interesting piece of information.

Please replace paragraph [0031] with the following amended paragraph:

[0031] It was recently discovered that the administration of secretin, a gastrointestinal peptide hormone, to children diagnosed with ~~Autism~~ autism resulted in ameliorating the symptoms associated with ~~Autism~~ autism. This finding was published in the article by Horvath et al., entitled *Improved Social and Language Skills After Secretin Administration In Patients with Autistic Spectrum Disorders, Journal of the Association for Academic Minority Physician* Vol.9 No.1, pp. 9-15, January, 1998. The secretin administration, as described in Horvath, was performed as a diagnostic procedure, i.e., to stimulate pancreaticaobiliary secretion during an upper gastrointestinal endoscopy, rather than as a therapeutic procedure. Although the specific mechanism by which the secretin improved the autistic-related symptoms was not specifically identified, Horvath postulated that secretin may have had a direct or indirect effect on the central nervous system. What is important, however, is that this was the first time that gastrointestinal problems of autistic children were linked to a possible etiology in ~~Autism~~ autism.

Please replace paragraph [0033] with the following amended paragraph:

[0033] Accordingly, in view of such findings, a method for determining whether an individual suffering from a dysautonomic disorder and/or any disorder comprising ~~dysautonmic~~ dysautonomic components will benefit from the administration of secretin, other neuropeptides, peptides and/or digestive enzymes, would be highly advantageous. In addition, a method for aiding in the diagnosis of individuals who may develop ~~dysatonomic~~ dysautonomic disorders ~~and~~, conditions and symptoms is highly desirable.

Please replace paragraph [0034] with the following amended paragraph:

[0034] The present invention is directed to methods for aiding in the diagnosis of ~~dysautonomic~~ dysautonomic disorders and dysautonomic conditions, and for treating individuals diagnosed as having dysautonomic disorders or dysautonomic conditions ~~including~~ including, but not limited to, Familial ~~Dystautonomia~~ Dysautonomia (FD) (or Riley-Day Syndrome), Guillaine-Barre Syndrome (GBS) (or acute idiopathic ~~polyneuorpathy~~ polyneuropathy), Parkinson's disease, fetal fatal insomnia (FFI), diabetic cardiovascular neuropathy, Heredity Sensory and ~~autonomic~~ Autonomic ~~nueropathy~~ Neuropathy type III (HSAN III), central autonomic disorders including ~~Parkinson's and~~ multiple system atrophy (Shy-Drager syndrome), orthostatic intolerance syndrome including mitral ~~value~~ valve prolapse, postural tachycardia syndrome (POTS), and idiopathic hypovolemia, dysautonomic syndromes and disorders of the ~~catecholemine~~ catecholamine family including baroreflex failure, dopamine-B-Hydroxylase deficiency, pheochromocytoma, chemodectina, familial paraganglioma syndrome, tetrahydrobiopterin deficiency, aromatic-L-amino acid decarboxylase deficiency, Menke's disease, monoamine oxidase deficiency states, and other disorders of dopamine metabolism, dysautonomic syndromes and disorders of the cardiovascular system, Chaga's disease, Diabetic ~~autonome~~ autonomic failure, pure autonomic failure, syncope, hypertension, cardiovascular disease, renal disease and SIDS.

Please replace paragraph [0037] with the following amended paragraph:

[0037] In another aspect, a method for treating a ~~dyautonomic~~ dysautonomic disorder with secretin comprises the step of administering to an individual having the disorder an effective amount of secretin to improve a symptom of the disorder.

Please replace paragraph [0039] with the following amended paragraph:

[0039] In another aspect, the stool compound comprises a pancreatic enzyme such as chymotrypsin, or any compound that provides an indication of either ~~protien~~ protein digestion or metabolism, pancreatic function, or an inflammatory process, or a combination thereof.

Please replace paragraph [0044] with the following amended paragraph:

[0044] FIG. 3 is a table diagram illustrating measured chymotrypsin levels of a plurality of ~~indivudials~~ individuals, some of which ~~having~~ have a dysautonomic condition.

Please replace paragraph [0045] with the following amended paragraph:

[0045] The present invention is directed to methods for aiding in the diagnosis of ~~dysuatonomic~~ dysautonomic disorders and dysautonomic conditions, and for treating individuals diagnosed as having a dysautonomic disorder such as Familial ~~Dystautonomia~~ Dysautonomia and other disorders having dysautonomic components. In a preferred embodiment, a method is provided for determining the presence of abnormal protein digestion and/or pancreatic dysfunction of an individual, especially a child, by analyzing a stool sample of the individual for the ~~quanititave~~ quantitative levels of one or more pancreatic enzymes, including, but not limited to, chymotrypsin, so as to determine if the individual has, or can develop, a dysautonomic disorder or condition. Further, a method is provided for determining whether the individual is likely to benefit from the administration of secretin, CCK, VIP, digestive enzymes, and/or other peptides and/or neuropeptides. Until now, there has been no clear biological marker for ~~dysautonic~~ dysautonomic disorders or conditions to allow early diagnosis or screening of such disorders or conditions.

Please replace paragraph [0046] with the following amended paragraph:

[0046] As noted above, it was recently discovered that the administration of secretin, a gastrointestinal peptide hormone, to children diagnosed with ~~Autism~~ autism resulted in ameliorating the symptoms associated with ~~Autism~~ autism. Subsequently, the inventor herein discovered that a sub-population of autistic children had~~, e.g.,~~ abnormal to pathologic levels of a pancreatic enzyme such as chymotrypsin in their stools. The inventor herein further discovered that the sub-population of autistic children who had low levels of fecal ~~chymotryypsin~~ chymotrypsin were positive responders to a therapeutic method for treating autism comprising administration of~~, e.g.,~~ secretin and/or digestive enzymes. It was further discovered that a sub-population of individuals suffering from ADD (attention deficit disorder) and/or ADHD (attention deficit hyperactivity disorder) who had low levels of fecal ~~chymotryypsin~~ chymotrypsin were positive responders to a therapeutic method comprising administration of~~, e.g.,~~ secretin and/or digestive enzymes. These findings are described in detail in U.S. Patent Application Serial No. 09/466,559, filed December 17, 1999, entitled "Methods For Treating Pervasive Development Disorders," and U.S. Patent Application Serial No. 09/707,395, filed on November 7, 2000, entitled "Methods For Treating Pervasive Development Disorders", both of which are commonly owned and incorporated herein by reference.

Please replace paragraph [0047] with the following amended paragraph:

[0047] It has also been discovered by the present inventor that populations of autistic children suffer from GI disturbances and other conditions which are dysautonomic in nature. Moreover, as explained below, and in accordance with the present invention, it has been discovered by the inventor herein that a population of individuals suffering from dysautonomic disorders such as FD and Parkinson's have abnormal or pathologic levels of pancreatic enzymes such as chymotrypsin in their stools. Thus, these findings are believed to indicate a possible link between the etiology of autism, ADD, ADHD and autonomic dysfunction. For example, it is postulated that in dysautonomic syndromes, the partial paresis of the gastrointestinal tract, and therefore the

lack of functioning of the secretory cells of the proximal small intestine, preclude the proper formation and or release of secretin. It is further postulated that this abnormal protein digestion as reflected by the low levels of pancreatic enzymes such as chymotrypsin, can be improved by the administration of secretin, CCK, VIP, other neuropeptides, peptides and/or digestive enzymes to thereby ameliorate the ~~symptomotologies~~ symptomatologies of dysautonomic conditions. Indeed, as low measures of fecal chymotrypsin, for example, expresses an abnormality of protein digestion and/or pancreatic dysfunction, it is postulated that an improvement of protein digestion to promote normal growth and development of an individual suffering from a dysautonomic disorder or dysautonomic condition by the administration of secretin, CCK, VIP, other neuropeptides and/or peptides and/or digestive enzymes, can ameliorate the dysautonomic symptomatologies.

Please replace paragraph [0048] with the following amended paragraph:

[0048] The following case studies support the above findings. Further, preferred methods for diagnosing and treating dysautonomic disorders and ~~dyautonomic~~ dysautonomic conditions in accordance with the invention are described. It is to be understood that these examples are set forth by way of illustration only, and nothing therein shall be taken as a limitation upon the overall scope of the invention.

Please replace paragraph [0055] with the following amended paragraph:

[0055] A 6 year old male child previously diagnosed with Familial Dysautonomia presents with marked autonomic dysfunction, including a total inability to walk or talk. The child lacked fine motor movements, and underwent an autonomic crisis 5-7 times per day, which necessitated continuous skilled nursing, with life support equipment including a respirator in close proximity. The child was fed with a food pump, and had to have his bowel evacuated by hand due to the near total ~~anestitzation~~ anesthesization of the small and large intestines. Fundal Plication was performed in order to deduce the incidence of reflux, and excessive drooling was continually

present. The child was completely dependent upon his care givers, and was classified during his first year of life as having autistic qualities.

Please replace paragraph [0056] with the following amended paragraph:

[0056] The child was administered ongoing secretin infusions. A preferred secretin infusion process includes the initial step of prepping an arm of the individual with an IV injection of saline. A test dose of 1 U of, e.g., Secretin-Ferring is then administered to the individual. Approximately one minute after infusion, the ~~indivudual~~ individual is examined for signs of allergic reaction including rash, increased heart rate, and increase of blood pressure. If the individual does not display any signs of allergic reaction, the remaining units of Secretin-Ferring is administered to the individual in the manner of an IV push, which is then followed by a saline flush. Subsequently, the individual receives a 1-2 U/kg of body weight infusion of Secretin-Ferring via an IV push method approximately every 4 weeks for 8 months.

Please replace paragraph [0057] with the following amended paragraph:

[0057] It is to be understood that any commercially available form of secretin may be used. Furthermore, treatment of a dysautonomic condition can be made by the administration of an effective amout of secretin, neuropeptide, CCK,VIP, peptides and or digestive enzymes through one of intravenous, transdermal, intranasal, small molecule or a combination thereof, or other ~~siutable~~ suitable methods of administration.

Please replace paragraph [0065] with the following amended paragraph:

[0065] 4 children were administered secretin in the amount of 1 U/kg. Table 1 below demonstrates the changes observed where "BP" denotes is blood pressure and FC ~~dentotes~~ denotes fecal chymotrypsin level. As shown in Table 1, a significant decrease in blood pressure

was observed in each child immediately after the administration of secretin. Additionally, a flush similar to that of niacin sensitivity was observed in 3 children.

Please replace paragraph [0068] with the following amended paragraph:

[0068] In summary, the results of the case studies described herein demonstrate that ~~dysautomonie~~ dysautonomic disorders may be treated with the ~~admininstration~~ administration of secretin, CCk, VIP, and other neuropeptides and peptides and/or digestive enzymes. Furthermore, the results indicate that the quantitative level or activity of pancreatic enzymes in a stool sample, such as fecal chymotrypsin, can be used to determine if an individual has, or can develop, one or more dysautonomic disorders or conditions. Further, pancreatic enzymes such as chymotrypsin can be used as biological markers to determine the efficacy of administering secretin, CCk, VIP, and other neuropeptides and peptides and/or digestive enzymes to an individual having a dysautonomic disorder or condition to thereby treat the individual. Indeed, the above case studies indicate that the administration of secretin, CCK, VIP, and other neuropeptides and peptides and/or digestive enzymes to such individuals having, for example, sub-normal to pathologic levels of fecal chymotrypsin, will result in the amelioration of symptomatologies of such disorders.